Received: 13 March 2020 | Accepted: 7 April 2020

DOI: 10.1111/hae.14015

COMMENTARY

Haemophilia WILEY

World Federation of Hemophilia Gene Therapy Registry

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We are at an exciting juncture in the treatment of haemophilia. The first gene therapy product for patients with haemophilia could receive regulatory approval as soon as August 2020, with several other products close on the horizon. Gene therapy carries the potential for a 'functional cure of haemophilia', with bleeding essentially eliminated in the majority of treated patients for the duration of multi-year follow-up reports to date.[1-3] This is a dream that has been in the making since the cloning of the *F8* and *F9* genes in the early 1980s.[4-9]

Although the potential for these transformative gene therapies is huge, emerging technologies by definition have some unknowns in their safety and efficacy profiles.[10] Such novel therapies are usually evaluated and approved based on a small number of treated individuals. Most phase I-II gene therapy clinical trials in haemophilia enroll less than 30 patients and current phase III trial protocols plan for enrolment of 40-134 patients.[11] For a long lasting, potentially life long, therapy, mandated follow-up by the FDA is only 5 years, a relatively short time.[12] This imposes a heavy reliance on the postmarketing surveillance to gather critical post-therapy evidence of safety and durable efficacy.[10]

Some data will come from open-label extensions of ongoing phase III and future phase IV clinical trials; however, much of the burden will be on registry studies to amass long-term data on a large cohort of patients. While clinical trial data provide reassurance of short-term safety and efficacy of specific gene therapy products, we are entering this new treatment era with limited experience of the longer-term impact of gene therapy. Ultimately, the accumulation of patient exposure captured in longitudinal registries is the most robust means of revealing unexpected or rare events associated with

this new technology class. Detecting low incident or delayed safety events, particularly in small treatment cohorts of a rare disease, necessitates that each patient who receives gene therapy be followed over the long term, preferably their lifetime.

Our current knowledge leaves many unanswered questions about the safety and long-term efficacy of gene therapy.[10,13-16] These gaps in evidence dictate that we must all contribute to strengthening the evidence base. This data collection/surveillance effort should be a shared responsibility. Healthcare providers and patients will need to work together to collect standardized data on patients who receive gene therapy, ensuring that their experiences are captured in a registry, over their entire lifetime. Such longer-term data will assist regulators and manufacturers who are also closely monitoring signals of potential safety events and may provide assistance to payers regarding the efficacy and potential safety milestones needed to inform their reimbursement strategies.

Surveillance in rare diseases such as haemophilia necessitates a global reach, as patients who receive gene therapy will be dispersed throughout many countries and continents.[17] A global strategy is required to ensure a large enough patient pool to allow robust evaluation and detection of low-incident events that may otherwise go undetected. If events are captured in disparate registries or databases, it would be more complex, laborious, technically challenging and ultimately slower to combine the data. Such delays should be avoided at all cost. As the overall field of gene therapy continues to make progress, a growing set of long-term safety and efficacy data will ultimately define the future of gene therapy in haemophilia.

Integrating the collection of data into the clinical practice of physicians and the daily lives of patients requires a harmonious and uniform data collection methodology that will be accepted and used by all stakeholders. Only through cohesive efforts by all treating physicians, patients, regulatory agencies and manufacturers worldwide, will we be successful in ensuring gene therapy is safe and efficacious for our patients today, and in the future.

Through a collaboration with the International Society of Thrombosis and Hemostasis (ISTH), the European Haemophilia Consortium (EHC), the US National Hemophilia Foundation (NHF), the American Thrombosis and Hemostasis Network (ATHN), industry gene therapy development partners and Regulatory liaisons, the WFH has formulated a world Gene Therapy Registry (WFH GTR), that aims to collect a standardized set of core data, developed with input from a multi-stakeholder steering committee. The aim of the WFH GTR project is to provide a robust, scientifically valid data collection avenue, available to all healthcare providers treating patients who receive gene therapy. The WFH GTR will collaborate with individual haemophilia treatment centres and existing gene therapy registries to leverage established data repositories. A patient mobile application will allow integrating patient-reported outcomes directly into the WFH GTR. The data stemming from the WFH GTR will provide for robust ongoing surveillance of safety and efficacy.[8] We are now expanding our outreach for the WFH GTR to the provider and patient communities with implementation of the registry to begin later in 2020.

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